Diagnostic accuracy of ^{18}F-PSMA-1007 PET/CT for prostate cancer in primary staging and biochemical recurrence with different serum PSA levels: A systematic review and meta-analysis

Xue Liu[1]* MD,
Qi Wang[2]* MD,
Bao Zhang[3] MD,
Tao Jiang[3] MD,
Wenbing Zeng[1] MD

**These authors contributed to the work equally and should be regarded as co-first authors*

1. PET-CT centre, Chongqing University Three Gorges Hospital, Chongqing, China
2. Jishou University School of Medicine,Hunan, China
3. Department of Nuclear Medicine, The First Pepole's Hospital of Huaihua City, Hunan, China

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Corresponding author:
Wenbing Zeng MD,
PET-CT centre, Chongqing University Three Gorges Hospital,
165 Xincheng Road, Wanzhou,
404000, Chongqing,China.
422817593@qq.com

Tao Jiang MD,
Department of Nuclear Medicine,
The First Pepole,s Hospital of Huaihua City,
144 Jinxi South Road,
Huaihua,418000, Hunan, China.
wind212@qq.com

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Abstract

Objective: We performed a systematic review and meta-analysis to evaluate the application value of fluorine-18-prostate specific membrane antigen (^{18}F-PSMA-1007) positron emission tomography/computed tomography (PET/CT) in patients with different serum prostate specific antigen (PSA) levels and primary prostate cancer (PCa) or the biochemical recurrence of Pca. **Methods:** A comprehensive electronic literature search of the PubMed, Embase and Cochrane Library databases was conducted in accordance with the PRISMA statement. We calculated the pooled sensitivity and specificity of ^{18}F-PSMA-1007 PET/CT in PCa. A summary receiver operator characteristic (SROC) curve and the area under the curve (AUC) were used to assess the accuracy of ^{18}F-PSMA-1007 PET/CT for PCa. **Results:** The final analysis included 11 studies that described 799 patients and 4261 lesions with ^{18}F-PSMA-1007 PET/CT in PCa. The pooled sensitivity and specificity of ^{18}F-PSMA-1007 PET/CT in PCa were 0.836 and 0.946, respectively. The per-patient pooled sensitivity and specificity of ^{18}F-PSMA-1007 PET/CT in PCa were 0.934 and 0.453, and the per-lesion values were 0.816 and 0.979, respectively. The pooled sensitivity and specificity of ^{18}F-PSMA-1007 PET/CT in PCa with PSA>2ng/mL were 0.923 and 0.442 in a patient-based analysis and 0.799 and 0.961 in a lesion-based analysis, respectively. The pooled sensitivity and specificity of ^{18}F-PSMA-1007 PET/CT in PCa with PSA≤2ng/mL were 0.832 and 0.277 in a patient-based analysis, respectively. **Conclusion:** This meta-analysis showed that ^{18}F-PSMA-1007 PET/CT has a higher diagnostic value for prostate cancer in the setting of primary PCa and biochemical recurrence. As serum PSA levels increase, the diagnostic accuracy of ^{18}F-PSMA-1007 PET/CT also improves.

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Introduction

According to the World Health Organization (WHO), there were 1,276,106 new cases of prostate cancer (PCa) in 2018, affecting 13.5% of men, which represents the second-highest cancer incidence [1]. The pathogenesis of PCa involves multiple factors, including age, virus infection and genetic susceptibility [2]. Patients with PCa lack specific clinical symptoms during the early stages of the disease; as a result, when PCa is diagnosed, the majority of patients are at an advanced stage and the tumor is no longer resectable [3]. Therefore, it is particularly important to detect and treat PCa early.

After primary radiation therapy and radiation therapy with androgen deprivation therapy, the definition of biochemical recurrence (BCR) is serum prostate-specific antigen (PSA) levels of more than 0.2ng/mL or PSA increases of more than 2.0ng/mL compared to the lowest level after radiotherapy [4]. Whether patients with BCR have experienced clinical local recurrence or distant metastasis is key to making further treatment plans. Some studies have confirmed that patients with early BCR with low PSA levels have a better prognosis if they receive personalized treatment [5]. Traditional imaging examinations, such as bone scintigraphy (BS), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET/CT), have limited sensitivity for the detection of BCR of PCa [6, 7], especially for patients with low PSA levels.

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein with glutamate carboxypeptidase activity [8]. Prostate-specific membrane antigen expression is highly upregulated in advanced, metastatic, and poorly differentiated PCa and increases with tumor aggressiveness; it is usually 100 to 1000 times higher in PCa cells than in normal prostate cells [9]. Fluorine-18-PSMA-1007 (^{18}F-PSMA-1007) PET/CT is an advanced imaging modality used to assess PCa. Compared with MRI, BS and other tradi-

tional modalities, ^{18}F-PSMA-1007 PET/CT has a higher sensitivity, specificity and early detection rate of metastases [10].

In ^{18}F-PSMA-1007 PET/CT, physiological uptake can be seen in the salivary glands, liver, gallbladder, prostate, kidney and small intestine; additionally, concentrated foci with localized abnormal radioactivity uptake are considered positive, such as avid uptake in lymph nodes and bones, which can be diagnosed as metastases [11]. Currently, ^{18}F-labeled PSMA imaging agents include N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-^{18}F-fluorobenzyl-L-cysteine (^{18}F-DCFBC), 2-(3-{1-carboxy-5-[(6-[(^{18})F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid (^{18}F-DCFPYL) and ^{18}F-PSMA-1007[11]. Among them, a major advantage of ^{18}F-PSMA-1007 is its hepatobiliary excretion, while ^{18}F-DCFBC and ^{18}F-DCFPYL are mainly excreted through the urinary system.

Some single-center trials have suggested that ^{18}F-PSMA-1007 PET/CT is highly valuable for detecting primary lesions and biochemical recurrence in prostate cancer. Anttinen et al. (2020) [10] performed a non-randomized, prospective, single-institutional trial that compared the diagnostic accuracy of advanced imaging modalities with that of traditional modalities in the primary staging of men with high-risk PCa. They concluded that ^{18}F-PSMA-1007 PET/CT had a diagnostic accuracy of 0.89 for high-risk PCa at the patient level and 0.91 for bone metastasis level. One study [12] analyzed 251 patients, and 204 (81.3%) had evidence of recurrence on ^{18}F-PSMA-1007 PET/CT. The detection rates were 94.0% (79/84), 90.9% (50/55), 74.5% (35/47), and 61.5% (40/65) for PSA levels greater than or equal to 2, 1 to less than 2, 0.5 to less than 1, and 0.2 to less than 0.5 ng/mL, respectively. German researchers [13] used ^{18}F-PSMA-1007 PET/CT to analyze 100 cases of pathologically confirmed biochemically recurrent prostate cancer. The rates of pathological scans were 86%, 89%, 100% and 100% among patients with PSA levels ≤0.5, 0.51-1.0, 1.1-2.0 and >2.0ng/mL, respectively. However, these studies have relatively small sample sizes, regional differences and different PSA levels, so their conclusions were highly heterogeneous.

Therefore, the purpose of this meta-analysis and systematic review was to evaluate the application value of ^{18}F-PSMA-1007 PET/CT in patients with different serum PSA levels and primary PCa or the biochemical recurrence of Pca.

Methods

This meta-analysis was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. This study was registered in the PROSPERO database (registration number: CRD42021281741).

Data sources and search strategy

We performed electronic literature searches of the PubMed, Embase and Cochrane Library databases for English-language articles from the earliest available date of indexing through 28 February 2021. We also manually searched the reference lists of the identified publications to identify additional studies. The following key words were used for the selection of studies: PSMA, prostate-specific membrane antigen, prostate cancer, prostate recurrence, positron imaging, PET and ^{18}F-PSMA-1007.

Study selection

The inclusion criteria for the relevant studies were as follows: (a) ^{18}F-PSMA-1007 PET/CT was used to identify and characterize PCa; (b) subjects were diagnosed with PCa by histopathology, imaging examinations or clinical follow-up; (c) either sufficient data to calculate sensitivity and specificity of ^{18}F-PSMA-1007 PET/CT in PCa or absolute numbers of true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN) were reported; and (d) analyses were performed on a per-patient or per-lesion basis.

The exclusion criteria were as follows: (a) overlapping papers; (b) review articles, animal experiments, editorials or letters, comments and conference proceedings; (c) a lack of access to the full text; (d) insufficient data to reassess sensitivity and specificity from individual studies; and (e) a sample size of fewer than 10 patients with PCa or PCa lesions.

Data extraction

A data abstraction sheet was developed. Two researchers (XL, TJ) independently assessed the collected data that included basic information (authors, publication year, and country), study design (prospective or retrospective), patient characteristics, sample size (patients or lesions), blinding method (yes or no), imaging agent (^{68}Ga-PSMA-11 or ^{18}F-PSMA-1007), imaging modality (PET/CT or MRI), agent dosage, level of PSA, and diagnostic criteria for characterizing PCa. Each study was analyzed to retrieve the number of TP, TN, FP, and FN according to the reference standard. Only studies providing all of this information were included in final the meta-analysis. In cases of disagreement, a consensus was reached on inclusion or exclusion by discussion, and if necessary, a third researcher (BZ) was consulted.

Quality assessment

The methodological quality of the included studies was critically appraised based on the modified Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) [14, 15], as recommended by the Cochrane Collaboration. Each item was evaluated as "high", "low" or "unclear". Each paper was scored independently by two evaluators (XL and TJ), and any discrepancies were resolved.

Statistical analysis and data synthesis

All data from each eligible study were extracted. Descriptive statistics such as the mean and standard deviation are used to summarize continuous variables, while count and percentage are used for categorical variables. The primary objective was to estimate the sensitivity, specificity, positive likelihood ratio (PL+), negative likelihood ratio (LR+) and diagnostic odds ratio (DOR) with a 95% confidence interval (95% CI). A DOR can be calculated as the ratio of the odds of positivity of a disease state relative to the odds of positivity of the non-disease state, with higher values indicating a better discriminatory test performance [16]. A bivariate normal random-effects model for measures was used to analyze and pool the diagnostic performance of previous studies [17]. This method accounts for variation occurring between studies as well as the correlation between sensitivity and specificity. Each data point of the sum-

mary receiver operator characteristic (SROC) graph was extracted from an individual study; then, an SROC curve was generated based on these points, and the smoothed curve revealed the pooled accuracy [18]. The area under the curve (AUC) of the SROC was calculated to measure the accuracy of ^{18}F-PSMA-1007 PET/CT, MRI and ^{68}Ga-PSMA-11 PET/CT for diagnosing patients with PCa or PCa lesions. The I-square statistic was calculated, and the Cochrane Q test was performed to test for statistical heterogeneity between the studies on the basis of random-effects analysis [19]. Publication bias was examined using an effective sample size funnel plot and the associated regression test of asymmetry, as described by Deeks and colleagues (2005) [20]. When there was substantial statistical heterogeneity, we performed subgroup analysis to identify potential sources of bias [21]. Tests for significance were two-tailed, with a statistically significant P-value threshold of 0.05. All statistical analyses were carried out using the commercial software programs Meta-Disc 1.4 (Hospital Universitario Ramony Cajal, Madrid, Spain) and Review Manager 5 software (Review Manager 2014).

Results

Literature search and study selection

After a comprehensive computerized search was performed and the reference lists were extensively cross-checked, our study identified 168 records (PubMed=64, Cochrane Library=4, and Embase=100). After reviewing titles and abstracts, 116 records were excluded because they were non-human studies, duplicated reports, reviews, editorials, conference abstracts or small case series. Additionally, 37 unrelated abstracts were removed. By reading the full texts, 4 articles were eliminated because of a lack of sufficient information to calculate sensitivity and specificity. Finally, 11 studies met all the inclusion (and none of the exclusion) criteria and were included in this systematic review and meta-analysis. No other articles were found after screening the references of these articles. The detailed procedure implemented for article selection in the meta-analysis is presented in Figure 1.

Characteristics of the included studies

The major characteristics of the 11 studies [10, 12, 13, 22-29] included in the meta-analysis are described in Table 1. The eleven articles were published between 2017 and 2021, including eight retrospective studies (75%) [12, 13, 22-27] and three prospective studies (25%) [10, 28, 29]. Five studies [10, 22, 23, 26, 29] assessed the primary initial staging of prostate cancer. All studies used PET/CT as an imaging modality. Three studies [10, 22, 26] simultaneously evaluated ^{18}F-PSMA-1007 PET/CT and MRI. The imaging agents ^{18}F-PSMA-1007 and ^{68}GA-PSMA-11 were compared simultaneously in two studies [25, 29]. One study compared ^{18}F-PSMA-1007 with ^{18}F-fluorocholine (FCH) [28]. Most of the research was from Germany (67%), and the other studies were from Poland [28], Finland [10], the Netherlands [26] and Israel [29].

The number of cases in each study ranged from 10 to 251. There was a total of 799 PCa patients and 4261 PCa lesions in the included studies, and the ages of the patients ranged from 46 to 88 years. The serum PSA levels ranged from 0.08 to 250ng/mL. We conducted all analyses based on per-patient and/or per-lesion data.

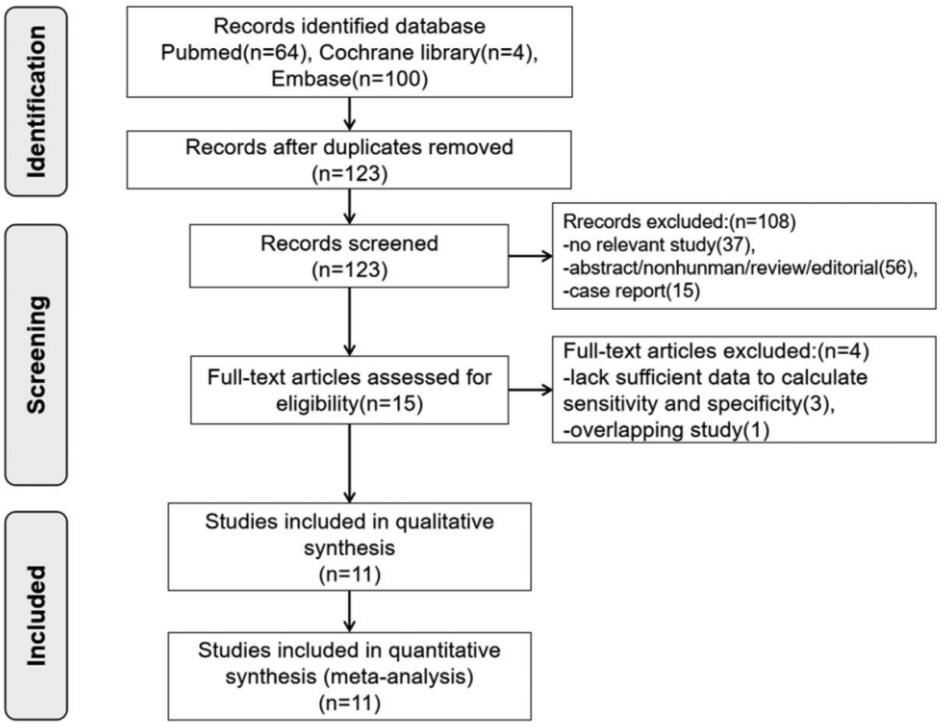


Figure 1. Flow chart of the search for eligible studies on ^{18}F-PSMA-1007 PET/CT in patients of prostate cancer.

Table 1. *Characteristics of the included studies.*

Author	Publication year	Country	Patients/ lesion（n）	Mean/Median Age(year)	Blined	Mean/Median PSA （ng/mL）	GS score	Imaging Modality	Imaging agent (Activity)	Study type	PET/CT Purpose	Positive diagnostic criteria
Kesch [22]	2017	Germany	10/372	Median:67(62-77)	Yes	Median: 13.1(5.8-40.0)	NG	PET/CT, MRI	^{18}F-PSMA-1007 (NG)	R	Primary Staging	MRI/TRUS-guided fusion biopsy /conventional TRUS biopsy
Rahbar [13]	2018	Germany	100/NG	Mean: 68.75±7.6	No	Mean: 3.36±6.11	NG	PET/CT	^{18}F-PSMA-1007 (4 MBq/kg)	R	Biochemical relapse	Focal tracer uptake above local background in morphologically visible lesions on CT was considered as PSMA-positive
Giesel [12]	2019	Germany	251/NG	Median:70(48-86)	No	Median: 10.9 （0.6–250）	NG	PET/CT	^{18}F-PSMA-1007(301±6.46 MBq)	R	Localizing recurrent prostate cancer	Focal uptake higher than the surrounding background and not associated with physiologic uptake
Witkowska-Patena [28]	2019	Poland	40/NG	Mean:69 ± 7	NG	Mean: 0.77±0.61	Mean: 7.1±1	PET/CT	^{18}F-PSMA-1007(296±14 MBq), ^{18}F-FCH(248±35MBq)	P	Evaluation and localization of biochemical relapse	At least 1 lesion highly suggestive of malignancy
Anttinen[10]	2020	Finland	79/1581	Mean:70±7	Yes	Median: 12(7–23)	NG	PET/CT, MRI	^{18}F-PSMA-1007(NG)	P	Primary Staging	Imaging modalities, clinical follow-up (including PSA kinetics and, histopathological specimens)

(continued)

Sprute [23]	2021	Germany	96/1746	Median:69.5(48-78)	NG	Median: 10.5(0.1-120)	NG	PET/CT	^{18}F-PSMA-1007(270 MBq)	R	Primary Staging	Pathology
Sachpekidis [24]	2020	Germany	25/NG	Median:66(48–84)	NG	Median: 1.2（0.2-237.3）	NG	PET/CT	^{18}F-PSMA-1007(237 MBq)	R	Evaluation biochemical recurrence or progression	Follow-up(imaging modalities and clinical)
Rauscher [25]	2020	Germany	102/371	Mean:71.6±8	NG	Median: 0.87（0.20-13.59）	Range:6-10	PET/CT	^{18}F-PSMA-1007(325±6.4MBq), ^{68}Ga-PSMA-11(47±6.27 MBq)	R	Assess detection efficacy	Focal tracer uptake above local background in morphologically visible lesions on CT was considered as PSMA-positive
Privé [26]	2020	Netherlands	53/46	NG	NG	Median: 12(7.7-20)	NG	PET/CT, MRI	^{18}F-PSMA-1007(250 MBq)	R	Primary Staging	Multi-parametric MRI and histopathology
Kuten [29]	2019	Israel	16/145	Median:68.5 (62.7-71)	NG	Median: 6.35(5.1-10.9)	Range:7-8	PET/CT	^{18}F-PSMA-1007, ^{68}Ga-PSMA-11(NG)	R	Primary Staging	Histopathology,Immuno histochemical
Ceriani [27]	2020	Germany	27/NG	67.2±7.8	NG	Median: 1.4(0.3-27.7)	NG	PET/CT	^{18}F-PSMA-1007(159±31MBq)	R	Biochemical relapse	Histopathology ,MRI,Follow-up,PET/CT

PSA=prostate-specific antige, PSMA=Prostate-specific membrane antigen, PCa=prostatic cancer, P=Prospective, R=Retrospective, NG=Not given, TRUS=transrectal ultrasound, PET/CT=positron emission tomography/computerized tomography, MRI=magnetic resonance imaging, GS=Gleason score.

Risk of bias and applicability

The risk of bias and applicability concerns for the included studies was assessed using QUADAS-2, as shown in Figure 2 and the Supplementary Table 1. All included studies were of moderate to high quality.

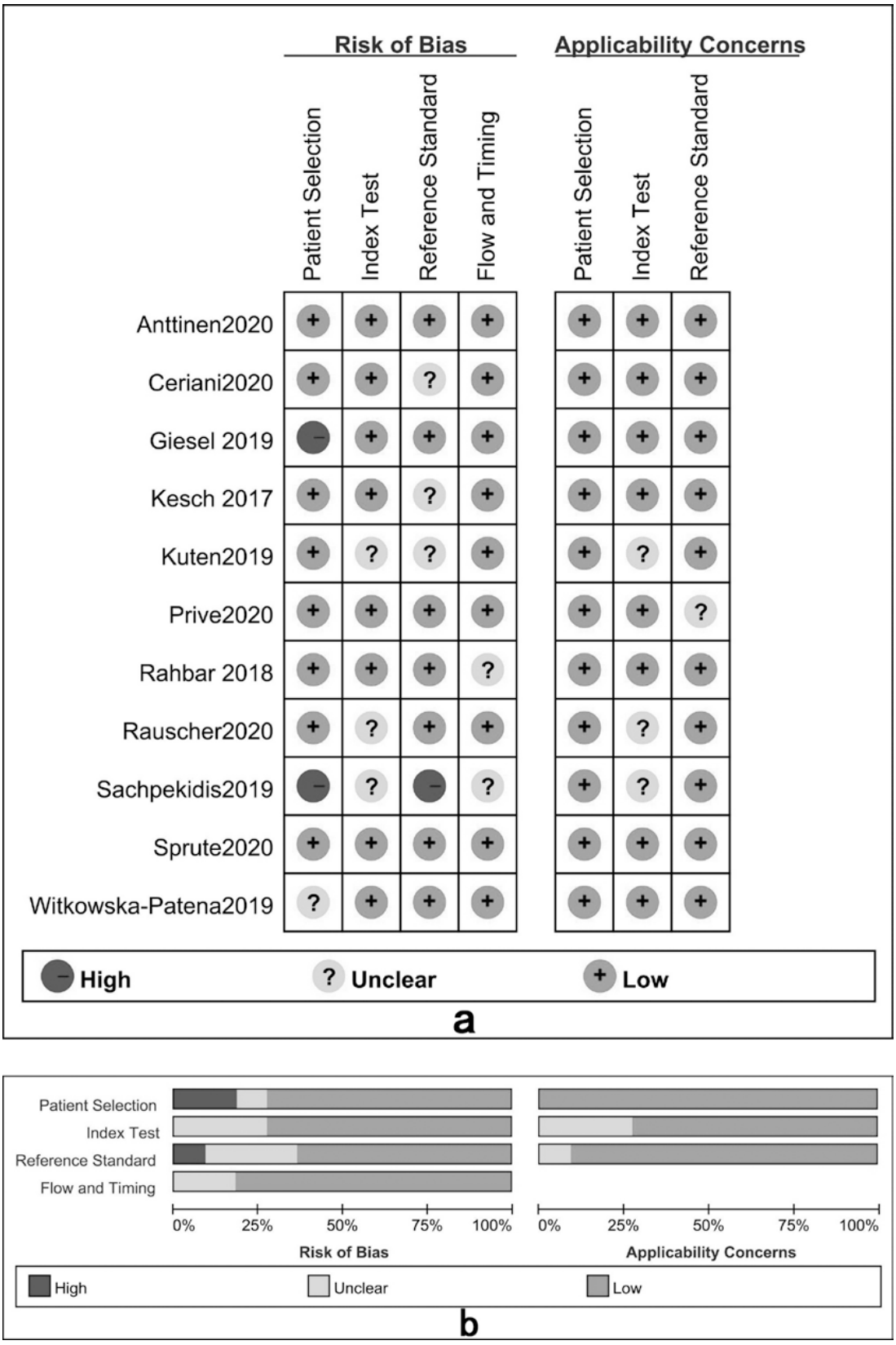


Figure 2. Risk of bias and applicability concerns summary (a) and graph (b) of the studies included in the systematic review according to the QUADAS-2 tool.

Quantitative analysis (meta-analysis)

The diagnostic value of ^{18}F-PSMA -1007 PET/CT results from 11 studies was performed with quantitative analysis (Supplementary Table 2). The sensitivity and specificity values of ^{18}F-PSMA-1007 PET/CT ranged from 0.55 to 0.99 and from 0.28 to 1.00, with pooled estimates of 0.836 (0.812-0.858) and 0.946 (0.938-0.953), respectively. The area under the summary ROC curve was 0.9468. The included studies showed statistical heterogeneity in their estimate of the diagnostic odds ratio (I2: 94.3%).

To reduce heterogeneity, subgroup analyses accounting for the different PSA levels (PSA>2 or PSA≤2), imaging modality (PET/CT or MRI), radiotracer (^{18}F-PSMA-1007 or ^{68}Ga-PSMA-11), imaging purposes (primary staging or BCR) and analyzed objects (patient or lesion) were performed. When ^{18}F-PSMA-1007 PET/CT was applied in the initial stage of PCa, the combined sensitivity, specificity and AUC were 0.783 (0.748-0.814), 0.978 (0.972-0.983) and 0.9616, respectively. The combined sensitivity, specificity and the AUC of ^{18}F-PSMA-1007 PET/CT in the biochemical recurrence of PCa after comprehensive therapy were 0.925 (0.894-0.949), 0.706 (0.660-0.748) and 0.9857, respectively (Figure 3 and Supplementary Figure 1). The combined sensitivity, specificity and AUC of ^{18}F-PSMA-1007 PET/CT in PCa were 0.934 (0.874-0.971), 0.453 (0.389-0.519) and 0.9762 in a patient-based analysis and 0.816 (0.787-0.844), 0.979 (0.974-0.984) and 0.9335 in a lesion-based analysis, respectively.

When PSA>2ng/mL, the pooled sensitivity and specificity of ^{18}F-PSMA-1007 PET/CT in PCa were 0.923 (0.854-0.966) and 0.442 (0.377-0.510) in a patient-based analysis and 0.799 (0.762-0.833) and 0.961 (0.950-0.970) in a lesion-based analysis, respectively (Figure 4 and Supplementary Figure 2). The AUC of ^{18}F-PSMA-1007 PET/CT in PCa were 0.5 (per patient) and 0.9593 (per lesion) for PSA>2ng/mL. When PSA≤ 2ng/mL, the pooled sensitivity, specificity and AUC of ^{18}F-PSMA-1007 PET/CT in PCa were 0.832 (0.771-0.883), 0.277 (0.217-0.343) and 0.8557 in a patient-based analysis, respectively. Due to insufficient data, it was not possible to perform a meta-analysis on a per-lesion basis for ^{18}F-PSMA-1007 PET/CT in PCa when PSA≤2ng/mL.

Among the included studies, 3 studies simultaneously compared the application value of MRI in PCa. These studies only analyzed focus-based data when PSA>2ng/ml. Therefore, the pooled sensitivity, specificity and AUC of MRI in PCa were 0.570 (0.518-0.621), 0.917 (0.903-0.930) and 0.8427, respectively (Figure 5).

According to the AUC value and SROC curve, the ranking of the value of different imaging agents or imaging devices for the evaluation of PCa is ^{18}F-PSMA-1007 PET/CT, MRI, and ^{68}Ga-PSMA-11 PET/CT, in increasing order (Figure 6).

Publication bias

In this meta-analysis, there was no publication bias in the included studies according to Deek's test, and the bias of the test was -13.90 (P=0.64). In addition, Deek's funnel plot, a symmetry test, was symmetric (P=0.42), also indicating that publication bias was absent.

Discussion

Radical prostatectomy, external beam radiotherapy and endocrine therapy are the main treatment methods for prostate cancer [30]. Up to 40% of patients develop BCR during their lifetime, and approximately 25% develop clinical recurrence after 7-8 years [31]. Therefore, the accurate detection of recurrent lesions is of great importance for improving the success rate of salvage therapy. PSMA is highly overexpressed by prostate cancer cells, up to 100- or 1000-fold above the levels in normal cells. It is expressed at the highest levels in poorly differentiated, metastatic, and hormone-refractory prostate cancer. It has become a new molecular target for the diagnosis and treatment of prostate cancer [32, 33].

Fluorine-18-PSMA-1007 PET/CT has important application

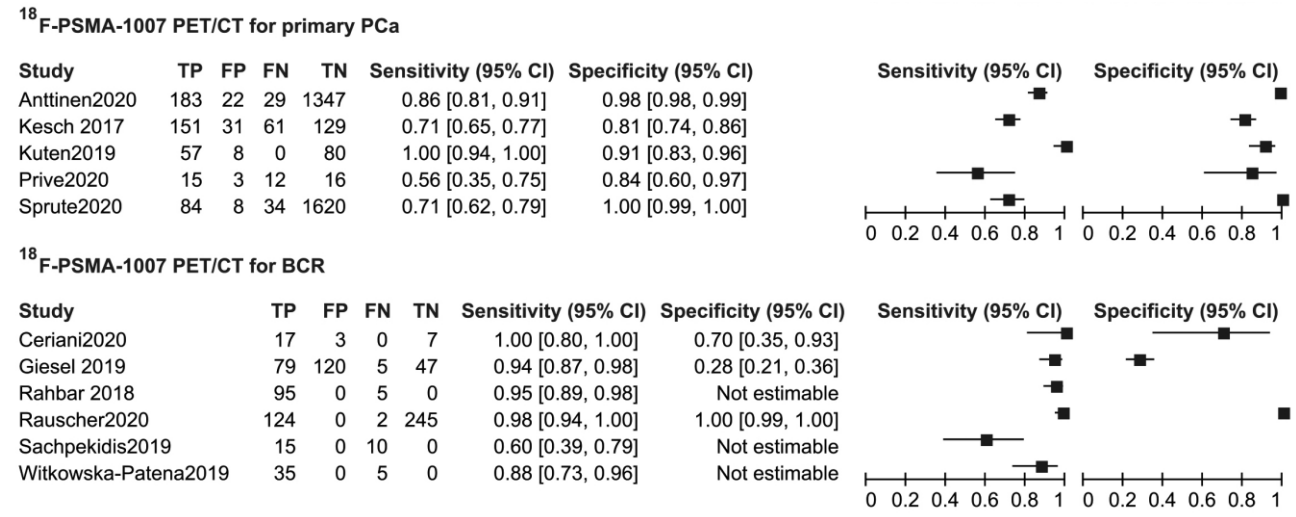


Figure 3. Forest plot of ^{18}F-PSMA-1007 PET/CT for primary PCa or BCR. PCa=prostate cancer; BCR=biochemical recurrence; TP=true positive; TN=true negative; FP=false positive; FN=false negative; PSMA=prostate-specific membrane antigen; CI=confidence interval.

^{18}F-PSMA1007 PET/CT-patient

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Anttinen2020	17	6	3	53	0.85 [0.62, 0.97]	0.90 [0.79, 0.96]
Ceriani2020	17	3	0	7	1.00 [0.80, 1.00]	0.70 [0.35, 0.93]
Giesel 2019	79	120	5	47	0.94 [0.87, 0.98]	0.28 [0.21, 0.36]
Rahbar 2018	95	0	5	0	0.95 [0.89, 0.98]	Not estimable
Rauscher2020	88	0	14	0	0.86 [0.78, 0.92]	Not estimable
Sachpekidis2019	15	0	10	0	0.60 [0.39, 0.79]	Not estimable
Witkowska-Patena2019	35	0	5	0	0.88 [0.73, 0.96]	Not estimable

^{18}F-PSMA1007 PET/CT-patient（PSA＞2ng/mL）

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Anttinen2020	17	6	3	53	0.85 [0.62, 0.97]	0.90 [0.79, 0.96]
Giesel 2019	79	120	5	47	0.94 [0.87, 0.98]	0.28 [0.21, 0.36]
Rahbar 2018	95	0	5	0	0.95 [0.89, 0.98]	Not estimable

^{18}F-PSMA1007 PET/CT-patient（PSA≤2ng/mL）

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Giesel 2019	50	149	5	47	0.91 [0.80, 0.97]	0.24 [0.18, 0.31]
Rahbar 2018	87	0	8	5	0.92 [0.84, 0.96]	1.00 [0.48, 1.00]
Witkowska-Patena2019	17	0	18	5	0.49 [0.31, 0.66]	1.00 [0.48, 1.00]

^{18}F-PSMA1007 PET/CT-lesion

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Anttinen2020	183	22	29	1347	0.86 [0.81, 0.91]	0.98 [0.98, 0.99]
Giesel 2019	137	0	154	0	0.47 [0.41, 0.53]	Not estimable
Kesch 2017	151	31	61	129	0.71 [0.65, 0.77]	0.81 [0.74, 0.86]
Kuten2019	57	8	0	80	1.00 [0.94, 1.00]	0.91 [0.83, 0.96]
Prive2020	15	3	12	16	0.56 [0.35, 0.75]	0.84 [0.60, 0.97]
Rauscher2020	124	0	2	245	0.98 [0.94, 1.00]	1.00 [0.99, 1.00]
Sprute2020	84	8	34	1620	0.71 [0.62, 0.79]	1.00 [0.99, 1.00]

^{18}F-PSMA1007 PET/CT-lesion（PSA＞2ng/mL）

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Anttinen2020	183	22	29	1347	0.86 [0.81, 0.91]	0.98 [0.98, 0.99]
Giesel 2019	137	0	154	0	0.47 [0.41, 0.53]	Not estimable
Kesch 2017	151	31	61	129	0.71 [0.65, 0.77]	0.81 [0.74, 0.86]
Kuten2019	57	8	0	80	1.00 [0.94, 1.00]	0.91 [0.83, 0.96]
Prive2020	15	3	12	16	0.56 [0.35, 0.75]	0.84 [0.60, 0.97]

^{18}F-PSMA1007 PET/CT-lesion（PSA≤2ng/mL）

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Giesel 2019	72	0	219	0	0.25 [0.20, 0.30]	Not estimable

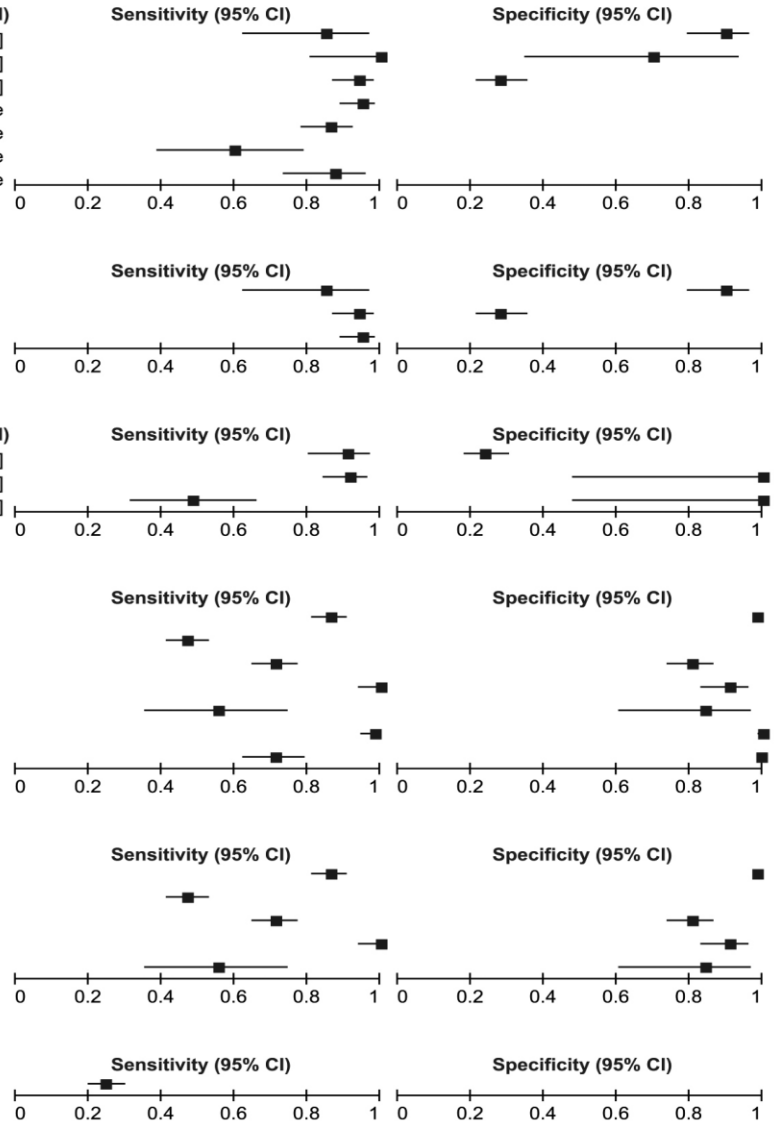


Figure 4. Forest plot of ^{18}F-PSMA-1007 PET/CT for patient/lesion with PCa at different serum PSA levels. PCa=prostate cancer; TP=true positive; TN=true negative; FP=false positive; FN=false negative; PSMA = prostate-specific membrane antigen; CI = confidence interval.

^{18}F-PSMA-1007 PET/CT

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Anttinen2020	183	22	29	1347	0.86 [0.81, 0.91]	0.98 [0.98, 0.99]
Ceriani2020	17	3	0	7	1.00 [0.80, 1.00]	0.70 [0.35, 0.93]
Giesel 2019	79	120	5	47	0.94 [0.87, 0.98]	0.28 [0.21, 0.36]
Kesch 2017	151	31	61	129	0.71 [0.65, 0.77]	0.81 [0.74, 0.86]
Kuten2019	57	8	0	80	1.00 [0.94, 1.00]	0.91 [0.83, 0.96]
Prive2020	15	3	12	16	0.56 [0.35, 0.75]	0.84 [0.60, 0.97]
Rahbar 2018	95	0	5	0	0.95 [0.89, 0.98]	Not estimable
Rauscher2020	124	0	2	245	0.98 [0.94, 1.00]	1.00 [0.99, 1.00]
Sachpekidis2019	15	0	10	0	0.60 [0.39, 0.79]	Not estimable
Sprute2020	84	8	34	1620	0.71 [0.62, 0.79]	1.00 [0.99, 1.00]
Witkowska-Patena2019	35	0	5	0	0.88 [0.73, 0.96]	Not estimable

^{68}Ga-PSMA-11 PET/CT

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kuten2019	54	1	9	81	0.86 [0.75, 0.93]	0.99 [0.93, 1.00]
Rauscher2020	126	193	0	52	1.00 [0.97, 1.00]	0.21 [0.16, 0.27]

MRI

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Anttinen2020	78	53	134	1316	0.37 [0.30, 0.44]	0.96 [0.95, 0.97]
Kesch 2017	113	75	18	133	0.86 [0.79, 0.92]	0.64 [0.57, 0.70]
Prive2020	20	4	7	15	0.74 [0.54, 0.89]	0.79 [0.54, 0.94]

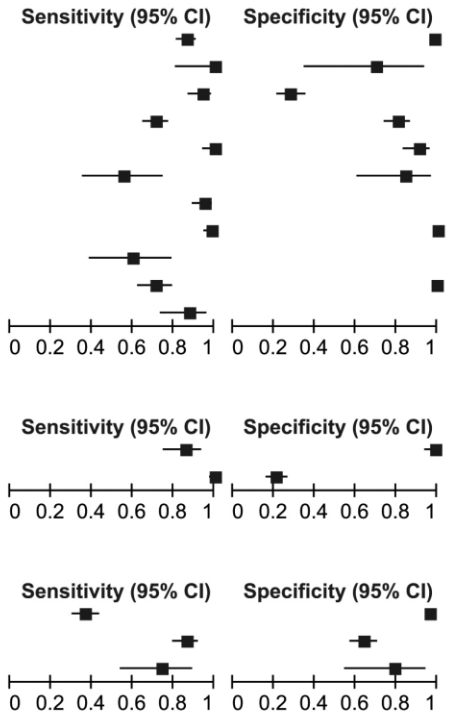


Figure 5. Forest plot of ^{18}F-PSMA-1007 PET/CT, ^{68}Ga-PSMA-11 PET/CT and MRI in prostate cancer. TP=true positive; TN=true negative; FP=false positive; FN=false negative; PSMA = prostate-specific membrane antigen; CI = confidence interval.

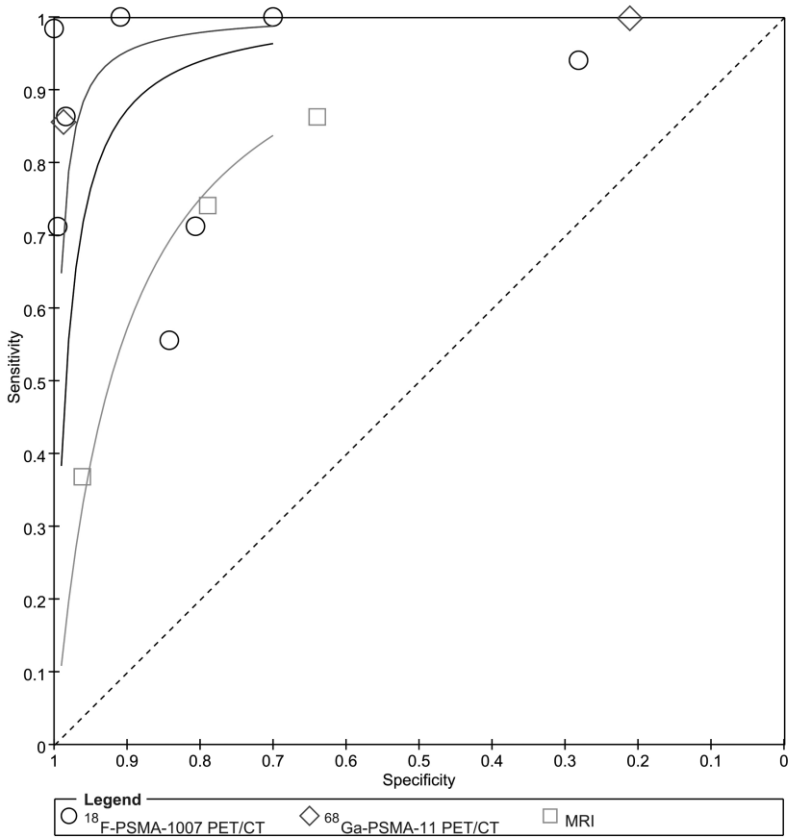


Figure 6. Summary receiver operator characteristic curve of ^{18}F-PSMA-1007 PET/CT, ^{68}Ga-PSMA-11 PET/CT and MRI in prostate cancer.

value for the assessment of the primary tumor stage and the biochemical recurrence of prostate tumors, especially for different serum PSA levels. However, due to the influence of various factors (sample size, region, etc.), the conclusions regarding its diagnostic efficacy have been inconsistent. Therefore, this study evaluated the application value of ^{18}F-PSMA-1007 PET/CT in prostate cancer in patients with different serum PSA levels by performing a meta-analysis and systematic review.

In the previously published meta-analyses [34-36], Treglia et al. (2019) [36] analyzed the detection rate of ^{18}F-labeled PSMA PET/CT for the biochemical recurrence of PCa. The imaging agents included were ^{18}F-PSMA-1007, ^{18}F-DCFPyL and ^{18}F-DCFBC. Four studies were included on the imaging agent ^{18}F-PSMA-1007, and the pooled detection rate was 89%. However, Treglia et al. (2019) [36] did not perform subgroup analyses for each radiotracer at different serum PSA levels nor analyses on the pooled sensitivity, specificity and AUC for ^{18}F-PSMA-1007 PET/CT in PCa.

Our meta-analysis revealed that ^{18}F-PSMA-1007 PET/CT had a higher diagnostic value for detecting primary tumors and screening for metastatic lesions in biochemical recurrence, with a sensitivity and specificity of 0.836 and 0.946, respectively. Furthermore, the AUC (0.9468) demonstrates that ^{18}F-PSMA-1007 PET/CT is an accurate diagnostic method in this setting. The higher detection rate may have been due to the superior differentiation of ureter and bladder activity associated with local recurrence and local lymph node metastasis [25]. The confidence regarding diagnoses of local recurrence is thus higher. Especially in patients with low PSA levels, radiotherapy for local recurrence may induce a second complete response [25].

This study found significant heterogeneity between studies for assessing sensitivity and specificity. To reduce possible sources of heterogeneity, subgroup analyses were performed according to different serum PSA levels, imaging agents, and imaging devices. Our results showed that the pooled sensitivity of ^{18}F-PSMA-1007 PET/CT in PCa was 93.4% (per patient) and 81.6% (per lesion), and the AUC were 0.976 (per patient) and 0.933 (per lesion), respectively. In addition, this study also analyzed the ability of ^{18}F-PSMA-1007 PET/CT to detect lesions in patients with different serum PSA levels, and its ability was dependent on PSA levels. Due to the limited number of included references, data could be combined only when the cut-off was 2ng/mL. Therefore, the combined sensitivity, specificity and AUC of ^{18}F-PSMA-1007 PET/CT for patients with PCa were 92.3%, 96.1% and 95.9, respectively, when PSA>2ng/mL. When PSA≤2ng/mL, the combined parameters were all lower than those when PSA>2ng/mL. Therefore, as serum PSA levels increase, the ability of ^{18}F-PSMA-1007 PET/CT to detect lesions becomes stronger, and this is in line with the results of a previous meta-analysis [37]. This may be related to tumor activity, number, and size; the site of metastasis (lymph node, bone tissue); and the expression level of PSMA in lesions [37, 38].

Due to its high sensitivity, specificity and predictive value for the evaluation of the prostate, multiparameter MRI (mp-MRI) has been applied with an increasing frequency worldwide [39]. In addition to detecting structural and anatomical changes in the prostate, the technique provides insights into potential malignancy through parameters such as diffusion restriction. The use of mp-MRI also appears to increase the proportion of clinically relevant prostate cancer that is diagnosed. This technique is also more accurate than CT for assessing lymph nodes within the pelvis [40]. However, while MRI is a useful advance, it is still limited by issues, such as claustrophobia, cost, and views that are often confined to the pelvis [40]. In our analysis, three studies [10, 22, 26] simultaneously compared the diagnostic value of ^{18}F-PSMA-1007 PET/CT and MRI in primary prostate cancer. The application of MRI was analyzed in a per-lesion analysis for patients with PSA>2ng/mL. The combined sensitivity, specificity and AUC of MRI in PCa were 57%, 91.7% and 84.27, respectively. Based on the comparison of the combined parameters, the diagnostic efficacy of ^{18}F-PSMA-1007 PET/CT was higher than that of MRI. In a study Privé et al. (2020) [26] of 53 patients with primary prostate cancer, ^{18}F-PSMA-1007 PET/CT correctly staged seminal vesicle invasion (i.e., pT3b) more often than mp-MRI (90 vs. 76%), whereas mp-MRI more accurately detected extracapsular extension (i.e., pT3a) than ^{18}F-PSMA-1007 PET/CT (90 vs. 57%). Anttinen et al. (2020) [10] hypothesized that ^{18}F-PSMA-1007 PET/CT had superior sensitivity and higher interreader agreement than MRI. The value of ^{18}F-PSMA-1007 PET/CT for bone metastasis is obviously higher than that of BS, CT, single-photon emission computed tomography (SPECT) and whole-body MRI. The authors [10] suggested that ^{18}F-PSMA-1007 PET/CT increases the detection of low-volume metastatic disease. Kesch et al. (2017) [22] used ^{18}F-PSMA-1007 PET/CT and mp-MRI to examine 10 high-risk PCa patients, and the PPV and accuracy were 91% and 93%, while that of mp-MRI was 91% and 87%, respectively. This shows that ^{18}F-PSMA-1007 PET/CT shows promise for accurate local staging.

Two studies synchronously compared the application of ^{18}F-PSMA-1007 and ^{68}GA-PSMA-11 in the biochemical recurrence of PCa in our study. There were too few comparative studies to accurately determine which method was superior. Rahbar et al. (2018) [13] suggested that ^{18}F-PSMA-1007 has higher sensitivity than ^{68}GA-PSMA-11. Our study also found that the sensitivity of ^{18}F-PSMA-1007 was higher than that of ^{68}GA-PSMA-11 (0.952 vs.0.816) based on PCa lesions. Rauscher et al. (2020) [25] showed that ^{18}F-PSMA-1007 PET/CT had the same detection rate in recurrent prostate cancer based on patient analysis. The authors noted that it was more likely to detect recurrent lesions closer to the bladder wall. The detection rate of ^{18}F-PSMA-1007 was slightly higher at low PSA levels, which may be related to the different energy distributions of the positron emitters ^{18}F and ^{68}Ga [12]. Theoretically, the resolution of ^{18}F is higher than that of ^{68}GA, especially in human PET systems [41]. Therefore, it could be posited that ^{18}F-labeled PSMA ligands might improve the detection sensitivity for very small tumors [12]. Surprisingly, they believed that the sensitivity of ^{18}F-PSMA-1007 PET/CT was significantly higher than that of ^{68}GA-PSMA-11; that is, the former could detect 5 times more benign lesions than the latter [25]. As stated by Awenat et al. (2021) [42], in the absence of histological validation, it cannot be excluded that some lesions detected with ^{18}F-PSMA-1007 PET/CT may represent false-positive findings. False positive findings may be due to benign lesions or other malignancies than PCa with

PSMA overexpression [10, 12]. Grünig et al.'s (2021) [43] study concluded that ^{18}F-PSMA-1007 PET/CT detected a specific uptake foci in bone in 51.4% of patients with prostate cancer. Common false-positive sources are non-specific physiological radiotracer uptake of the cervical, celiac, or sacral ganglia and unspecific uptake of healing rib fractures, lymph nodes (e.g., inguinal, axillary, or mediastinal) [25]. In addition, a recent study mentioned that the overall positive predictive value (PPV) of ^{18}F-PSMA-1007 PET/CT in prostate cancer biochemical recurrence was limited (86%), and the PPV of bone lesions (79%) was more modest compared to local recurrence (97%) or pelvic lymph node metastasis (93%) [44]. Due to the lower diagnostic performance of bone lesions, they hypothesized that ^{18}F-PSMA-1007 PET/CT carries a risk of misclassification in recurrent prostate cancer [44]. In particular, false-positive findings may lead to incorrect staging or require further diagnostic or invasive tests, such as additional imaging or biopsy. Further studies will need to demonstrate the extent of the clinical impact of uncertain bone lesions [45].

In addition, our meta-analysis evaluated the included studies using the QUADAS-2 tool, and the quality was medium to high. Deek's test was performed for all studies and suggested that there was no publication bias.

Our study has limitations. First, only two studies simultaneously compared and analyzed the application value of ^{18}F-PSMA-1007 and ^{68}GA-PSMA-11 in prostate cancer. Second, we did not obtain enough ^{18}F-PSMA-1007 PET/CT data from patients with lesions with PSA<2ng/mL, so the diagnostic efficacy was not evaluated under these circumstances. Third, partially positive lesions detected by ^{18}F-PSMA-1007 PET/CT could not be pathologically confirmed in prostate cancer biochemical recurrence after comprehensive therapy, so the false positive rate could not be evaluated. Therefore, our study included both primary and therapeutic biochemical relapses. Last, there was heterogeneity between the studies. Subgroup analyses were performed to reduce heterogeneity, but there was heterogeneity across subgroups. This may be related to differences in the study population, methods, quality and the general lack of appropriate reference criteria. In the future, more large-scale, high-quality and better-reported studies are required to address these shortcomings.

In conclusion, this meta-analysis concluded that ^{18}F-PSMA-1007 PET/CT had a higher diagnostic value for prostate cancer, including primary tumors and biochemical recurrence. As the serum PSA levels increase, the diagnostic accuracy of ^{18}F-PSMA-1007 PET/CT also improves.

The authors declare that they have no conflicts of interest.

Ethical approval

This article does not contain any study with human participants or animals performed by any of the authors.

Authors' contributions

XL and TJ were involved in data management and statistics, and drafted the manuscript. XL,TJ and BZ verified the extracted data following the literature search, monitored the study and drafted the manuscript. WBZ designed the current study. TJ and BZ conducted the searches and performed statistical analysis. XL and QW performed extracted the data and contributed to quality assessment. All authors contributed to drafting and revising the manuscript and all authors read and approved the final manuscript.

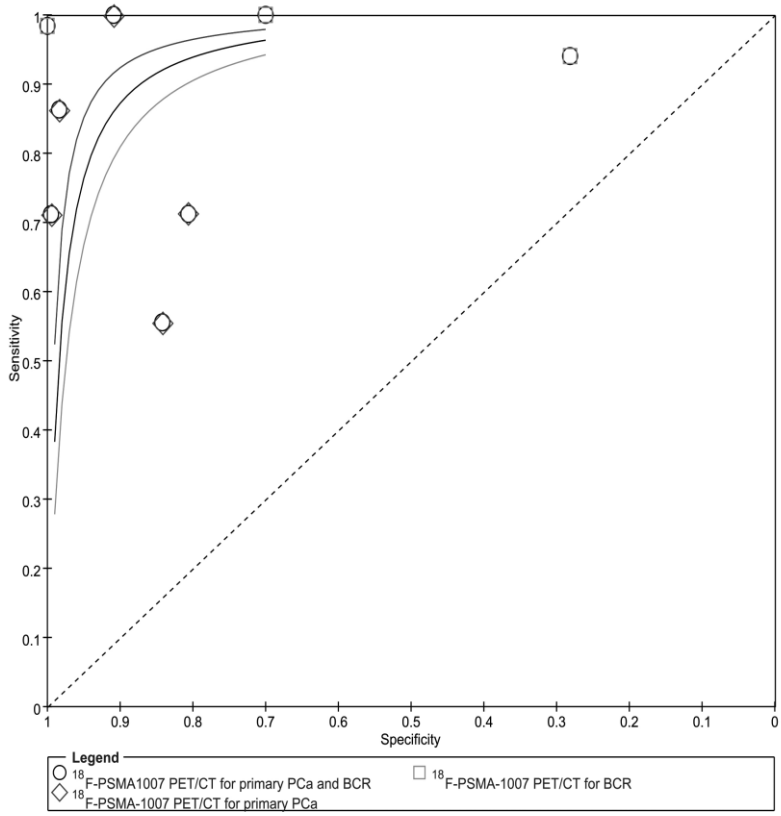
Supplementary Table 1. *Review of the quality of the studies included according to the Quality Assessment for Diagnostic Studies-2 (QUADAS-2) tool. Risk of Bias and Applicability Concern for patient selection, index test, reference standard, and flow and timing.*

	Risk of Bias				Applicability Concern		
Author	**Pt selection**	**Index test**	**Ref Std**	**Flow and timing**	**Pt Selection**	**Index Test**	**Ref Std**
Anttinen（2020）	low	low	low	low	low	low	low
Ceriani（2020）	low	low	unclear	low	low	low	low
Giesel （2019）	high	low	low	low	low	low	low
Kesch（ 2017）	low	low	unclear	low	low	low	low
Kuten（2019）	low	unclear	unclear	low	low	unclear	low
Prive（2020）	low	low	low	low	low	low	unclear
Rahbar （2018）	low	low	low	low	low	low	low
Rauscher（2020）	low	unclear	low	low	low	unclear	low
Sachpekidis（2019）	high	unclear	high	unclear	low	unclear	low
Sprute（2020）	low	low	low	low	low	low	low
Witkowska-Patena（2019）	unclear	low	low	low	low	low	low

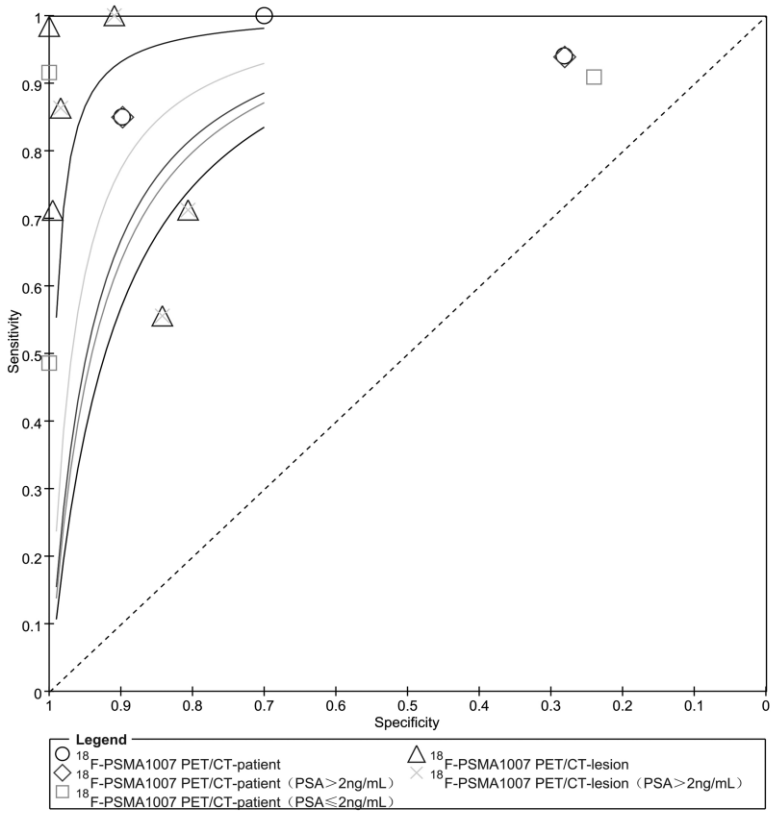
Supplementary Table 2. *The diagnostic efficacy of ^{18}F-PSMA1007 PET/CT, MRI and ^{68}Ga-PSMA-11 PET/CT in prostate cancer.*

Variable	Sen (95% CI)	Spe (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)	AUC
^{18}F-PSMA-1007 PET/CT -PPCa and BCR	0.836（0.812-0.858）	0.946（0.938-0.953）	7.554（1.509-37.809）	0.189（0.107-0.334）	59.833（12.952-276.40）	0.9468
^{18}F-PSMA-1007 PET/CT- PPCa	0.783（0.748-0.814）	0.978（0.972-0.983）	16.211（3.647-72.061）	0.255（0.140-0.466）	97.662（11.683-816.35）	0.9616
^{18}F-PSMA-1007 PET/CT -BCR	0.925（0.894-0.949）	0.706（0.660-0.748）	4.178（0.153-114.055）	0.127（0.031-0.526 ）	36.334（1.697-777.78）	0.9857
^{18}F-PSMA-1007 PET/CT-patient	0.934(0.874-0.971)	0.453(0.389-0.519)	3.126(0.746-13.106)	0.176(0.091-0.339)	21.747(3.814-124.01)	0.9762
^{18}F-PSMA-1007 PET/CT-lesion	0.816(0.787-0.844)	0.979(0.974-0.984)	23.527(5.580-99.201)	0.173(0.085-0.354)	204.10(26.731-1558.4)	0.9335
^{18}F-PSMA-1007 PET/CT-patient (PSA>2ng/mL)	0.923(0.854-0.966)	0.442(0.377-0.510)	3.204(0.398-25.798)	0.192(0.098-0.377)	16.270(2.066-128.14)	0.5
^{18}F-PSMA-1007 PET/CT-lesion (PSA>2ng/mL)	0.799(0.762-0.833)	0.961(0.950-0.970)	9.431(2.090-42.556)	0.220(0.085-0.568)	63.424(5.280-761.84)	0.9593
MRI-lesion (PSA>2ng/mL)	0.570(0.518-0.621)	0.917(0.903-0.930)	4.346(1.488-12.695)	0.367(0.152-0.886)	13.154(9.601-18.022)	0.8427
^{18}F-PSMA-1007 PET/CT-patient （PSA≤2ng/mL)	0.832(0.771-0.883)	0.277(0.217-0.343)	3.553(0.296-42.725)	0.277(0.090-0.858)	10.921(1.309-91.085)	0.8557
^{68}Ga-PSMA-11 PET/CT-lesion	0.952(0.912-0.978)	0.407(0.353-0.462)	9.240(0.001-131952.3)	0.073(0.008-0.666)	218.86(26.435-1812.0)	0.5

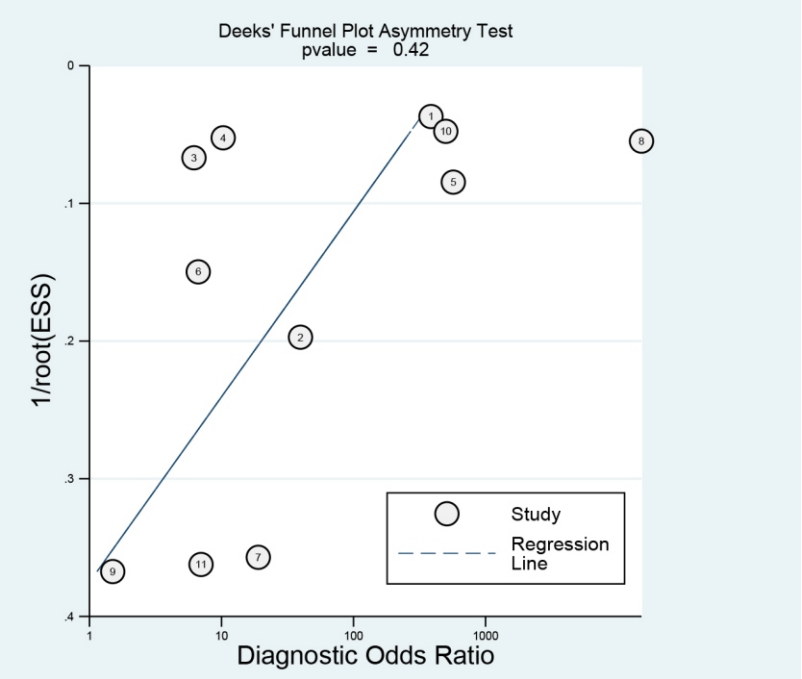
PPCa=primary prostatic cancer, BCR=biochemical recurrence, Sen=sensitivity, Spe=specificity, PL+=positive likelihood ratios, LR-=negative likelihood ratios, AUC=area under the curve, DOR=diagnostic odds ratios.95% CI =95% confidence interval.



Supplementary Figure 1. Summary receiver operator characteristic graph of ^{18}F-PSMA-1007 PET/CT for primary PCa and/or BCR. PCa=prostate cancer; BCR= biochemical recurrence; PSMA=prostate-specific membrane antigen.



Supplementary Figure 2. Summary receiver operator characteristic graph of ^{18}F-PSMA-1007 PET/CT for patient/lesion with PCa at different serum PSA levels. Pca=prostate cancer;PSMA = prostate-specific membrane antigen.



Supplementary Figure 3. Funnel plot with Deeks' test (P=0.42).

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